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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/625,047	MEARES ET AL.	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,8,10-24,26,27,30 and 33-42* is/are pending in the application.

4a) Of the above claim(s) *16-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6, 8, 10-15, 24, 26-27, 30 and 33-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 7/22/2008 in response to the previous Non-Final Office Action (1/22/2008) is acknowledged and has been entered.

Claims 1, 6, 8, 10-24, 26-27, 30 and 33-42 are pending.

Claims 16-23 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 1, 6, 8, 10-15, 24, 26-27, 30 and 33-42 are currently under consideration.

Rejections Withdrawn:

The rejection of Claims 6, 8 and 33-36 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of Applicants amendments.

The rejection of claims 1 and 37 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a subject with cancer by administration of a macrocyclic metal chelate, said method comprising the steps of: administering to said subject an antibody comprising an antigen recognition domain that recognizes said macrocyclic metal chelate, wherein said antibody comprises: a reactive site within the structure of the antibody that is not present in the wildtype of said antibody, wherein said reactive site is in a position within said antigen recognition domain and said antibody comprises a variable light chain region comprising the amino acid sequence of SEQ ID NO: 1 and variable heavy chain region comprising the amino acid sequence of SEQ ID NO: 5 or an antibody comprising CDR1, CDR2 and CDR3 of the VL chain of SEQ ID NO: 1 (SEQ ID NOs: 2, 3 and 4, respectively) and CDR1, CDR2, and CDR3 of the VH chain of SEQ ID NO: 5 (SEQ ID NOs: 6, 7 and 8 respectively), does not provide enablement for an antibody comprising a first sequence having at least 95% homology with SEQ IDNO: 1; a second sequence having at least 95% homology with SEQ ID NO: 5; wherein the antibody comprises a reactive site within the structure of the antibody that is not present in the wildtype of said antibody is withdrawn upon careful review and consideration of Applicants amendments.

Rejections Maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6, 8, 10-15, 24, 26-27, 30, 33-36 and 38-39 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al. (WO 99/66951, of record) in view of Chmura et al. (PNAS 2001; 98: 8480-8484, of record).

Hansen et al. teach a method of treating diseased tissues in a patient, comprising: (a) administering to a patient a bi-specific antibody or antibody fragment having at least one arm that specifically binds to a targeted tissue and at least one arm that specifically binds a targetable conjugate; (b) optionally, administering to said patient a clearing composition, and allowing said composition to clear non-localized antibodies or antibody fragments from circulation; and (c) administering to said patient a first targetable conjugate which comprises a carrier portion which comprises or bears at least one epitope recognizable by said at least one other arm of said bi-specific antibody or antibody fragment, and one or more therapeutic agents (page 58, claim 1 of WO document). With regards to the targetable conjugate's epitope, the WO document teaches (page 9, lines 30-33) that the epitope includes, but is not limited to, a hapten. With regards to the hapten, Hansen et al. teach (page 10, line 2 and page 34, lines 27-28) that haptens include, but are not limited to, chelators such as DPTA and DOTA. For example, the WO document teaches (page 35, lines 7-11) a method of treating CEA-expresing tumors, wherein a bi-specific antibody with at least one arm, which specifically binds to CEA, and at least one arm, which specifically binds the targetable conjugate whose hapten is a conjugate of yittruim-DOTA is administered to a patient. With regards to the bi-specific antibody which recognizes CEA and a metal chelate such as DOTA, the WO document teaches (page 10, lines 26-33) that the bi-specific antibody is generated by derivatizing an

anti-CEA F(ab')$_2$ mAB with a hydrazide-maleimide cross-linker and coupling said derivatized anti-CEA F(ab')$_2$ to an anti-chelate Fab'-SH. Moreover, Hansen et al. teach (page 24, lines 24-33) that chelators, such as DOTA, may be conjugated to the carrier portion of a targetable conjugate by generating a reactive functional group such as carbodiimide and coupling the carbodiimide to the peptides free amines. Thus, while Hansen et al. does not teach a macrocyclic metal chelate comprising four nitrogen atoms as shown in the formula of claim 6 or an S configuration DOTA, the referenced limitations are an inherent structural feature of DOTA as evidenced by Sigma-Aldrich (see attached document of record). Thus, the claimed antibody appears to recognize the same macrocyclic metal chelate as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that a product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Hansen et al. does not explicitly teach that that the antibody comprises a reactive site within the structure of the antibody that is not present in the wildtype of said antibody, wherein said reactive site is in a position within said antigen recognition domain. Nor does Hansen et al. teach that the macrocyclic DOTA contain a functional group which is reactive with the reactive site of the antibody.

Chmura et al. teach a method of producing antibodies having infinite affinity with a ligand, wherein the antibodies comprise a chemically reactive site such as a cysteine near the ligand-binding site of the antibody; and the ligand comprises an electrophilic substituent designed to form a stable thioether bond on reaction with the cysteine side chain of the antibody (Title and page 8480, 2nd column, 3rd full paragraph and 4th full paragraph). While the reference teaches that the chemical manipulation of affinity is applicable to other biological binding pairs, the antibody used was the anti-chelate antibody CHA255 and the ligand used was (S)-benzyl-EDTA-indium chelates since the anti-chelate antibody possess high affinity for (S)-benzyl-EDTA-indium chelates and exquisite specificity for these small molecules (page 8480, 2nd column, 3rd full paragraph and 4th full paragraph). In particular, the reference teaches that a slow rate of dissociation is particularly

important for in vivo targeting application, where a targeted therapeutic drug requires a long period on the target to be effective (page 8480, 2nd column, 1st full paragraph). However, the reference teaches that most natural antibodies, as well as engineered fragments, against small molecule possess only a single ligand binding site; and therefore, only remain bound to its ligand for an average period of a few minutes to a few hours (page 8480, 2nd column, 1st full paragraph). As such, the reference teaches that the surest way to prolong the lifetime of a complex is to make a covalent bond between its components (page 8480, 2nd column, 2nd full paragraph).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to modify the anti-chelate antibody and chelate, e.g., DOTA, used in the method taught by Hansen et al. in view of the teachings of Chmura et al.. One would have been motivated to do so because Chmura et al. teach a method of generating an antibody having infinite affinity for a ligand which is applicable for to other ligand binding pairs, wherein the antibody forms a covalent bond with the ligand which prolongs the lifetime of the complex. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the anti-chelate antibody and chelate, e.g., DOTA, used in the method taught by Hansen et al. in view of the teachings of Chmura et al., one would achieve a method of prolonging the lifetime of the complex at the target site in vivo.

In response to this rejection, Applicants assert the following points:

1) Hansen does not teach an antibody which either recognizes or irreversibly binds to a DOTA chelates. For example, Applicants assert that Hansen teaches a bi-specific antibody, with one arm binding to a peptide carrier attached to a metal chelate or chelating agent, wherein the carrier peptide is the hapten. As such, Applicants assert that the antibody is actually raised against, and recognizes, the peptide carrier portion of the targetable conjugate (in several examples the peptide), not the chelate (see for example, page 12, lines 3-6 and page 23, lines 4-8).

2) The combining of Chmura et al .with Hansen et al .to rectify the deficiencies of Hansen et al is improper. For example, Applicants assert that the Examiner states, "Hansen et al .does not explicitly teach that the antibody comprises a reactive site within the structure of the antibody that is not present in the wildtype of said antibody, wherein said reactive site is in a position within said antigen recognition domain. Nor does Hansen et al. teach that the macrocyclic DOTA contains a

functional group which is reactive with the reactive site of the antibody." Thus, Applicants assert that the Examiner is relying upon Chmura to rectify this deficiency, equating DOTA with the chelating agent of Chmura et al., EDTA and equating the process for covalently attaching DOTA to an antibody with the process for covalently attaching EDTA to an antibody. However, Applicants assert that these comparisons do not hold true. For instance, Applicants assert that EDTA and DOTA are structurally different compounds and the Examiner has not made any art of record indicating that EDTA and DOTA are viewed as equivalent or obvious variations of each other. In addition, Applicants assert that there is no mention in Chmura et al. that the linkers which covalently attach EDTA to the antibody would also function to covalently attach DOTA to an antibody. Moreover, Applicants assert that the Examiner is equating the antibody containing reactive sites to covalently bind EDTA with the invention. However, Applicants assert that the Examiner has not made of record any art indicating that the CHA255 antibody of Chmura et al .and the 2D12.5 antibody of the present invention are viewed as equivalent or obvious variants of each other. In particular, Applicants assert that Chmura et al. teaches covalent attachment of the chelate EDTA to an antibody with "high affinity" and "exquisite specificity" for (S)-benzyl-EDTA-eindium chelates (See Chmura, page 880, second column, third paragraph. In view of this, Applicants contend that it is highly unlikely that DOTA would be recognized by the antibody in Chmura et al. Assuming arguendo that the antibody of Hansen et al. recognized the metal chelate of Chmura et al., Applicants assert that the metal chelate would not be able to covalently bind since the metal chelate functional group in Chmura et al. would necessarily have been bound to the peptide (Hansen) instead of to the mutant reactive site of the antibody.

3) Hansen and Chmura et al .fail to provide the necessary motivation to incorporate Chmura's description of an antibody that forms a covalent bond with a metal chelate into the bispecific antibodies of Hansen et al. In particular, Applicants contend that the peptide hapten of Hansen does not covalently bind to the antibody, nor does Hansen identify a problem which could be ameliorated by covalently binding the peptide hapten to the antibody or speculate about the techniques to increase the binding to their targets. Similarly, Applicants contend that there is no suggestion in Chmura et al. to use the disclosed antibody or metal chelate with a bi-specific antibody, nor is there any suggestion in Chmura to incorporate a cyclic metal chelate such as DOTA into a covalent complex with a mutant antibody. As such, Applicants assert that tacking a single

element from a first reference and combining it with the teachings of another reference if there is no suggestion in either reference to make such a combination is improper. In addition, Applicants assert that combining Hansen et al. with Chmura et al .would require removing required elements of the antibody in Hansen et al. (the peptide from the peptide chelate-conjugate). In view of this, Applicants assert that combining Hansen et al. with Chmura et al .would require a change in teh function of Hansen et al. (removal of the chelate from teh peptide-chelate conjugate), thus there is no rationale to support a conclusion that Hansen et al. and Chmura et al. render the instantly claimed invention obvious. Further, Applicants assert that combining Hansen et al. and Chmura et al. would not allow one of skill in the art to "at once envisage" the claimed invention. For Example Applicants contend that when a reference broadly discloses a compound but does not specifically name a claimed compound, one of ordinary skill in the art must be able to "at once envisage the claimed compound before it will be deemed anticipated. See In re Petering, 301 F. 2d 676 (CCPA 1962). In the instant case, Chmura et al .describes the covalent attachment of EDTA to an antibody, not the metal chelate DOTA. Hansen et al .broadly discloses chelates such as DTPA and DOTA, but doe not describe an embodiment that includes DOTA covalently bound to an antibody. However, Applicants contend that there is no suggestion in Hansen as to why one of skill in the art would choose DOTA to combine with the teachings of Chmura. Moreover, Applicants assert that in view of the structural dissimilarities between EDTA and DOTA and the disablement of the peptide chelate conjugate to accommodate the teachings of Chmura, one of skill I the art would not be able to "at once envisage" the claimed invention upon combining the teachings of these two references. As such, Applicants contend that the only motivation for one of skill in the art to combine the teachings of the references is provided by the instant specification, which is impermissible hindsight.

4) There is no reasonable expectation of success in combining the two references since Hansen et al. does not teach an antibody recognizing a metal chelate. Accordingly, Applicants assert that one of skill in the art would have no expectation of success in practicing the claimed invention by combining Hansen et al. and Chmura et al., because one of skill would not expect to be able to disassemble the peptide-chelate-conjugate complex of Hansen et al. to successfully use its disclosed antibody with the metal chelate of Chmura et al.

These arguments have been carefully considered, but are not found persuasive.

In response to Applicants assertions pertaining to the teachings of Hansen et al., the Examiner acknowledges and does not dispute Applicants contention that Hansen et al. teach a bi-specific antibody, with one arm binding to a peptide carrier attached to a metal chelate or chelating agent, wherein the carrier peptide is the hapten, e.g., the antibody is actually raised against, and recognizes, the peptide carrier portion of the targetable conjugate (in several examples the peptide), not the chelate (see for example, page 12, lines 3-6 and page 23, lines 4-8). However, the Examiner recognizes that this is only one embodiment taught by Hansen and the antibody does not appear to be limited to just recognizing the carrier peptide. For example, Hansen et al. teach the following:

> The present invention provides a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable conjugate. The targetable conjugate comprises a carrier portion which comprises or bears at least one epitope recognized by at least one arm of the bi-specific antibody or antibody fragment. In a preferred embodiment, the epitope is a hapten. In an alternative embodiment, the epitope is a part of the carrier. (page 9, last paragraph bridging page 10)

In view of this, it is clear that Hansen et al. is not limited to a bispecific antibody, with one arm binding to a peptide carrier attached to a metal chelate as asserted by Applicants, but encompass's bispecific antibodies with one arm which recognizes the hapten itself. Moreover, Hansen et al. teaches that examples of recognizable haptens include, but are not limited to, chelators, such as DTPA, fluorescein isothiocyanate, vitamin B-12 and other moieties **to which specific antibodies can be raised** (emphasis added) (page 10, lines 1-4). Additionally, Hansen et al. teaches antibodies which recognize a metal-DOTA complex. For example, Hansen et al. teach the following:

> In still other embodiments, the bi-specific antibody-directed delivery of therapeutics or prodrug polymers to *in vivo* targets can be combined with bi- specific antibody delivery of radionuclides, such that combination chemotherapy and radioimmunotherapy is achieved. Each therapy can be conjugated to the targetable conjugate and administered simultaneously, or the nuclide can be given as part of a first targetable conjugate and the drug given in a later step as part of a second targetable conjugate. In one simple embodiment, a peptide containing a single prodrug and a single nuclide is constructed. For example,

> the tripeptide Ac-Glu-GIy-Lys-NH2 can be used as a carrier portion of a targetable conjugate, whereby SN-38 is attached to the gamma glutamyl carboxyl group as an aryl ester, while the chelate DOTA is attached to the epsilon amino group as an amide, to produce the complex Ac-Glu(SN-38)-GIy- Lys(DOTA)-NH2. The DOTA chelate can then be radiolabeled with various metals for imaging and therapy purposes including In-Ill, Y-90, Sm-153, Lu- 177 and Zr-89. **As the metal-DOTA complex may represent the recognizable hapten on the targetable conjugate, the only requirement for the metal used as part of the DOTA complex is that the secondary recognition antibody also used recognizes that particular metal-DOTA complex at a sufficiently high affinity. Generally, this affinity (log K~) is between 6-11** (emphasis added) (page 34, lines 13-31).

Thus, while the Examiner does not dispute Applicants contention that Hansen et al. teaches bispecific antibodies with one arm which binds to an epitope present in a peptide carrier which is conjugated to a metal chelate, the Examiner recognizes that Hansen et al. also teaches bispecific antibodies with one arm which recognize particular metal-chelate complexes such as DOTA with sufficiently high affinity.

In response to Applicants assertions pertaining to the combining of Chmura et al .with Hansen et al .to rectify the deficiencies of Hansen et al. is improper, the Examiner acknowledges and has carefully considered Applicants arguments, and finds it pertinent to point out that no statement on record was made by the Examiner equating DOTA and EDTA structurally, equating the process of covalently attaching DOTA to an antibody with the process of covalently attaching EDTA to an antibody or equating the antibody containing reactive sites to covalently bind EDTA to the claimed invention as asserted by Applicants. As such, these arguments are not deemed to be commensurate in scope with the instant rejection. Additionally, the majority of Applicants arguments appear to be directed to the exact incorporation of the teachings of Chmura et al .into the macrocyclic chelate and antibody taught by Hansen et al, see for example, Applicants arguments that there is no mention in Chmura et al. that the linkers which covalently attach EDTA to the antibody would also function to covalently attah DOTA to an antibody. However, the Examiner recognizes that it must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon

references, which make up the state of the art with regard to the claimed invention. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. (emphasis added) see In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, the Examiner recognizes that both references represent analogous teachings of antibodies having a binding affinity for metal chelates; and further, Chmura suggests a way of increasing the lifetime of the complex, e.g., antibody-metal-chelate, by incorporating a chemically reactive site near the ligand-binding site of the and incorporating a electrophillic substituent on the ligand which forms a stable bond on reacting with the reactive site of the antibody. In other words, those of skill in the art at the time the invention was made recognize that incorporation of a chemically reactive site near the ligand-binding site of the and incorporating a electrophillic substituent on the ligand which forms a stable bond on reacting with the reactive site of the antibody increases the lifetime of an antibody-metal-chelate complex.

In response to Applicants contention that Hansen and Chmura et al. fail to provide the necessary motivation to incorporate Chmura's description of an antibody that forms a covalent bond with a metal chelate into the bispecific antibodies of Hansen et al., the Examiner acknowledges and has carefully considered these arguments. However, the Examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that an "express, written motivation to combine must appear in prior art references before a finding of obviousness." See Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). For example, motivation to combine prior art references may exist in the nature of the problem to be solved (Ruiz at 1276, 69 USPQ2d at 1690) or the knowledge of one of ordinary skill in the art (National Steel Car v. Canadian Pacific Railway Ltd., 357 F.3d 1319, 1338, 69 USPQ2d 1641, 1656 (Fed. Cir. 2004)). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In the instant case, the Examiner recognizes that both references represent analogous teachings of antibodies having a binding affinity for metal

chelates; and further, Chmura suggests a way of increasing the lifetime of the complex, e.g., antibody-metal-chelate, by incorporating a chemically reactive site near the ligand-binding site of the and incorporating a electrophillic substituent on the ligand which forms a stable bond on reacting with the reactive site of the antibody. In other words, those of skill in the art at the time the invention was made recognize that incorporation of a chemically reactive site near the ligand-binding site of the and incorporating a electrophillic substituent on the ligand which forms a stable bond on reacting with the reactive site of the antibody increases the lifetime of an antibody-metal-chelate complex. Secondly, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). In the instant case, the beneficial result or advantage is the prolonged lifetime of the complex as taught by Chmura et al. As such, one of ordinary skill in the art would be motivated to combine the teaching of the references in view of Chmura et al. Regarding Applicants assertions with respect to one of skill in the art to "at once envisage" the claimed invention, the Examiner recognizes that Applicants appear to be inferring that Hansen discloses a plethora of metal-chelates; and provides no motivation to one of skill in the art to choose DOTA out of the plethora of metal chelates. However, the Examiner recognizes that a metal-DOTA complex is specifically recited by Hansen to which antibodies can be produced. Moreover, one of skill in the art of for example organic chemistry can envision a covalent bond between a cysteine of an antibody and reactive functional group on DOTA. As such, it is not a "stretch" for one of skill in the art to envision the compound taught by the combination of Hansen et al.. and Chruma as asserted by Applicants. With regards to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to Applicants assertions that there is no reasonable expectation of success in combining the two references since Hansen et al. does not teach an antibody recognizing a metal

chelate, the Examiner recognizes that, as set forth above, Hansen et al. does teach a bispecific antibody with one arm which recognizes an epitope on a hapten, wherein haptens include, but are not limited to, DOTA (see response supra). As such, these arguments have not been found persuasive.

New Rejections/Objections:

Claim Objections

Claims 6, 8 and 40-42 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case, Claim 1 from which claims 6, 8 and 40-42 depends, recites a macrocyclic chelate that is 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA), and comprises a reactive functional group with a reactivity complementary to said antibody reactive site. As such, DOTA is a specific structure which comprises a reactive functional group with a reactive complementary to said antibody reactive site. However, the claims 6, 8 and 40-42 do not appear to further limit what the reactive functional group, but attempt to broaden the chemical structure of DOTA which is a specific compound.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 37 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the instant case, Claim 37, which depends from claim 1, attempts to further limit the antibody of claim 1 to having a first sequence having at least 95% sequence identity with SEQ ID

NO: 1, and wherein said antibody has a second sequence having at least 95% sequence identity with SEQ ID NO: 5. However, it is unclear whether the antibody of claim 1 further includes the sequences defined in claim 37 or whether both sequences define 1) the antigen recognition domain that recognizes a macrocyclic metal chelate, 2) the targeting moiety that binds to a tumor associated of 3) define the antigen recognition domains individually.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6, 8, 10-15, 24, 26-27, 30 and 33-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (Federal register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3) and (see MPEP 2164).

In the instant case, the claim 1 is inclusive of a genus of bispecific antibodies comprising an antigen recognition domain that recognizes a macrocyclic chelate and a targeting moiety that specifically binds to a cell surface receptor or cell surface antigen on a cancer cell. Claim 37 further limits the antibody to having a first sequence having at least 95 % sequence identity to SEQ ID NO: 1 and a second sequence having at least 95% sequence identity to SEQ IDNO: 5. Thus, claim 1 and 37 broadly encompasses antibodies having variations within the 6 CDR regions, but are still capable of binding to a macrocyclic metal chelate and a tumor associated antigen. However, the written

description in this case only sets forth an isolated antibody or fragment thereof, comprising a first amino acid sequence that is 100% identical to SEQ ID NO: 1, and a second amino acid sequence that is 100% identical to SEQ ID NO: 5, wherein one arm of the antibody binds to a tumor antigen and a second arm binds to a tumor associated antigen or a macrocyclic metal chelate.

For example, the specification teaches that after inspection of the crystal structure of the 2D12.5, e.g., light chain of SEQ ID NO: 1 and heavy chain of SEQ ID NO: 5, bound to its hapten DOTA, a number of cysteine residues were introduced at positions 53, 54 and 55 of the heavy chain and position 53 of the light chain. The further teaches determining the scope of the monoclonal antibody, 2D12.5, e.g., light chain of SEQ ID NO: 1 and heavy chain of SEQ ID No: 5. In particular, the specification teaches that the monoclonal antibody 2D12.5 binds not only to Y-DOTA but also DOTA complexes of all the lanthanides. Thus while the specification teaches an isolated antibody or fragment thereof, comprising a first amino acid sequence that is 100% identical to SEQ ID NO: 1, and a second amino acid sequence that is 100% identical to SEQ ID NO: 5 and binds to Y-DOTA or all DOTA complexes with all of the lanthonides, the specification appears to be silent on the binding affinities to DOTA of other antibodies comprising a first amino acid sequence that is at least 95% identical to SEQ ID NO: 1 and a second amino acid sequence that is at least 95% identical to SEQ ID NO: 12, or alternatively, the binding affinities to DOTA of other antibodies comprising a heavy chain variable region comprising a single amino acid substitution in any one of CDR1, CDR2, and CDR3 of SEQ ID NO: 5, and a light chain variable region comprising a single amino acid substitution in any one of CDR1, CDR2 and CDR3 of SEQ ID NO: 1.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cNDA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63

USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of antibodies that encompass the genus that bind DOTA nor does it provide a description of structural features that are common to the antibodies. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of one species of antibody is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) of the encompassed genus of antibodies, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any

particular species). Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Therefore, only an isolated antibody comprising a first sequence that is 100% identical to SEQ ID NO: 1 and a second sequence that is 100% identical to SEQ ID NO: 5, wherein the antibody binds to DOTA , but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Therefore, No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Examiner
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